REMARKS

Applicants have received and reviewed the Office Action mailed October 29, 2001. Claims 1-3 and 9-11 are currently pending. Claims 1-3 and 9-11 were rejected in the Office Action. Applicants have amended claims 2 and 3. Claims 1 and 9 through 11 have been cancelled. New claims 33 through 48 have been added. All claim amendments and cancellations are made without prejudice or disclaimer. Applicants respectfully request reconsideration of the application as amended herein.

Interview

Applicants first would like to thank Supervisory Examiner Remy Yucel, Ph.D., and Primary Examiner David Guzo, Ph.D., for the courtesy extended during the interview held herein on January 17, 2002. Applicants found the interview to be informative and helpful in understanding the rejections, as is evidenced by the statement in the Interview Summary (Paper No. 21) that:

> "Discussion focused on the differences in vector stability between the '525 vectors and those of Applicant. Because the status of claim 2 in the after final submitted 16 August 2001 was ambiguous, it was agreed that the finality of the most recent Office Action would be withdrawn (while maintaining the same period for response)."

As agreed at the interview, Applicants include herewith as Exhibit A the exhibits that were discussed at the interview.

Withdrawal of Finality of Office Action

Applicants acknowledge, with thanks, receipt of the Withdrawal of Finality (Paper No. 21) relating to the Office Action mailed October 29, 2001, as agreed at the interview of January 17, 2002.

Information Disclosure Statement

Applicants acknowledge receipt of the initialed copy of the Form PTO-1449 submitted with the "Second Supplemental Information Disclosure Statement" filed herein on August 16, 2001. Also enclosed herewith is a new Supplement Information Disclosure Statement and Form PTO-1449 citing Wickham et al.'s International Patent Publication

WO 96/26281, published August 26, 1996.

Claim Rejection under 35 U.S.C. § 102(e)

The Office renewed the rejection of claims 1-3 and 9-11 under 35 U.S.C. § 102(e), asserting that the subject claims are anticipated by U.S. Patent 6,127,525 to Crystal et al. Applicants traverse the rejection, as set forth hereinafter.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed Cir. 1989). *See generally* MPEP §§ 2131, 2136 et seq.

The Office maintains that it has established a *prima facie* case for the inherency in Crystal of adenoviral vectors having a "desirable tropism for respiratory epithelium". (Office Action, page 4). Therefore, the Office asserts, the burden is shifted to applicants to point out any *structural differences* between the present invention and the prior art so as to patentably distinguish the present invention from the prior art. (Office Action, page 5).

Assuming for the sake of argument that the Office has established a *prima facie* case of inherency in Crystal of adenoviral vectors having desired tropism, applicants herein undertake to rebut such alleged inherency by pointing out structural and other differences between the present invention and the Crystal reference. Specifically, as discussed at the interview of January 17, 2002, applicants believe that a substantial difference in vector structure and vector stability exists between the chimeric vectors of the present invention and those of Crystal. (*See* Exhibit A, page A-9). Further, the structure of the chimeric vectors of the present invention results in significantly decreased raising of neutralizing antibodies as compared to wild-type serotype 5 adenovirus. (*See* Exhibit A, pages A-7, A-8).

Crystal teaches "[w]hen the coat protein is incorporated into an adenoviral vector, preferably the entire coat protein of one adenoviral serotype can be *substituted* with the entire coat protein of another adenoviral serotype . . . ." (Crystal, col. 11, lines 3-7 (emphasis added)). With specific reference to fiber protein, Crystal teaches "preferably the

fiber protein can be replaced in its entirety, or in part, with sequences of a fiber protein from a different serotype of adenovirus." (Crystal, col. 11, lines 56-59). With respect to chimeric adenoviruses comprising non-native fiber proteins (*i.e.*, fiber proteins from different serotypes of adenovirus), Crystal's teachings are essentially limited to chimeric adenoviruses based on serotype 5 in which the entire fiber protein of serotype 5 is switched for an entire fiber protein of serotype 7 (referred to in Crystal as the "5 base/7 fiber" vector). (Crystal, FIG. 1; col. 23, line 60 through col. 24, line 54; col. 24, line 57 through col. 25, line 27).

Applicants have amended claims 2 and 3 and added new claims 33 through 48, all of which recite a chimeric adenoviral vector having a capsid derived from a first adenovirus serotype (serotype 5 in some embodiments) and a part of a fiber protein of serotype 11, 14, 16, 21, 34, 35, or 50 substituted for a corresponding part of the fiber of the first adenovirus serotype, wherein the part of the fiber comprises a tail region of the fiber of the first adenovirus serotype at its N-terminus. Retention of the tail region of the first adenovirus serotype fiber helps promote stability in the interface between the chimeric fiber and the penton-base of the first adenovirus serotype. Support for these amendments and new claims can be found in the as-filed Specification at, for example, FIG. 7; page 9, lines 22-27; page 14, lines 7-15; page 35, lines 23-27; and page 40, lines 1-5.

Crystal's 5 base/7 fiber vector is structurally different from applicants' chimeric vectors in that Crystal's 5 base/7 fiber vector comprises an entire serotype 7 fiber substituted for the entire serotype 5 fiber, whereas the present invention comprises a chimeric fiber comprising a tail region of a first adenovirus serotype and other fiber domains derived from serotypes 11, 14, 16, 21, 34, 35, or 50. In some of the claimed embodiments, the first adenovirus serotype is serotype 5. This structural difference results in improved stability of the claimed vectors as compared to Crystal's 5 base/7 fiber vector because the serotype 7 fiber tail region is only about 57% homologous to the serotype 5 fiber tail region on the amino acid level, whereas the claimed adenoviruses comprise the intact serotype 5 (or other serotype) tail region. (*See*, Exhibit A, page A-9). Thus, the chimeric fibers of the claimed invention are better able to interact properly with the penton-base of the first serotype, resulting in greater stability as compared with Crystal's completely substituted fiber.

Applicants would like to take this opportunity to clarify an issue concerning the adenovirus serotypes (specifically, serotypes 50 and 51) discussed in the as-filed Specification, the exhibits discussed at the Interview of January 17, 2002, and the claims as amended herein. Through a clerical error, the serotype of the fiber described in the as-filed Specification and the Interview exhibits as serotype 51 (SEQ ID NO.: 42) is actually serotype 50. The reason for this is that applicants obtained all 51 human adenovirus serotypes from Dr. Jan de Jong of the Rijksinstitut voor Volksgezondheid en Milieuhygiene (RIVM) (the Netherlands' National Institute on Public Health and Environmental Protection) in May of 1998. At that time, the serotypes identified by Dr. de Jong as 50 and 51 had just been isolated and characterized by Dr. de Jong and had not been published. However, in December of 1999, Dr. de Jong published an article that made clear that the serotypes applicants had referred to as 50 and 51, based on Dr. de Jong's May 1998 documentation, were actually the reverse. (de Jong, J. Clin. Microbiology, vol. 37, pages 3940-3945). That is to say, applicants' references to serotype 51 fiber (SEQ ID NO.:42) in the as-filed Specification and the Interview exhibits actually correspond with de Jong's serotype 50. Applicants are working to obtain a copy of Dr. de Jong's aforementioned article, which will be cited in an additional Supplemental Information Disclosure Statement to be filed herein as soon as possible. Therefore, the claims, as amended herein, recite serotype 50 rather than serotype 51 to reflect the correct identification of the fiber (SEQ ID NO.:42) serotype. It is respectfully submitted that no new matter is added thereby because the change corrects a clerical error and does not modify or add to the substance of the as-filed Specification.

It is therefore respectfully submitted a clear structural difference exists between the fiber proteins of Crystal and those of the claimed invention, as amended. It is further submitted that this structural difference patentably distinguishes the present invention over Crystal because retention of the fiber tail region of the first serotype, as in the claimed invention, results in improved vector stability as compared with Crystal's vectors. Accordingly, withdrawal of the rejection is respectfully solicited.

Conclusion

Claims 2, 3, and 33 through 48 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. If questions exist after consideration of the foregoing, the Office is kindly requested to contact the applicants' representative at the address or telephone number below.

Respectfully submitted,

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Dated: February 28, 2002
SGH/le
Attachments: Version with Markings to Show Changes Made; Exhibit A

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VERSION WITH MARKINGS TO SHOW CHANGES MADE
37 C.F.R. § 1.121(c)(1)(ii)

IN THE CLAIMS:

Please cancel claim 1.

2. (Four Times Amended) A recombinant vector derived from an adenovirus comprising at least one ITR and a packaging signal having a first insertion site for a nucleic acid sequence of interest, and further having a second insertion site for functionally inserting a gene encoding a penton and/or hexon protein of a first serotype of adenovirus and having a third insertion site for a gene sequence encoding [at least]a part of a fiber protein of a second adenovirus of a second serotype, the second serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, a gene encoding a penton and/or hexon protein from the first adenovirus serotype inserted into the second insertion site, [the first adenovirus serotype less antigenic in a human than the second adenovirus serotype,]a gene sequence encoding [at least a]the part of a fiber protein of the second adenovirus serotype inserted into the third insertion site, the gene sequence encoding [at least a]the part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host and comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus.

3. (Amended) The recombinant vector of claim 2 [which is]wherein the recombinant vector comprises a plasmid.

Please cancel claims 9 through 11.

Please add the following new claims:

33. (New) A chimeric adenovirus comprising:

an adenoviral capsid derived from a first adenovirus serotype; and

a part of an adenoviral fiber derived from a second adenovirus serotype substituted for a corresponding part of a fiber of the capsid derived from the first adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, the part of the adenoviral fiber derived from the second adenovirus serotype comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus.

34. (New) The chimeric adenovirus of claim 33 wherein the first adenovirus serotype is serotype 5.

35. (New) A chimeric adenovirus comprising:

an adenoviral capsid derived from a first adenovirus serotype; and

a part of an adenoviral fiber derived from adenovirus serotype 35 substituted for a corresponding part of a fiber of the capsid derived from the first adenovirus serotype, the part of the adenoviral fiber derived from adenovirus serotype 35 comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus.

36. (New) The chimeric adenovirus of claim 35 wherein the first adenovirus serotype is serotype 5.

37. (New) A method for producing a chimeric adenoviral particle having a capsid derived from a first adenovirus serotype exhibiting a desired tropism and antigenicity determined by a part of a fiber of a second adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, the method comprising:

providing a recombinant vector derived from the first adenovirus serotype comprising at least one ITR, a packaging signal, an insertion site for a nucleic acid sequence of interest, and an insertion site for a gene encoding the functional part of a fiber protein of the second adenovirus serotype;

inserting into the recombinant vector the gene encoding the functional part of the fiber protein of the second adenovirus serotype, the functional part of the fiber protein comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus;

transfecting said vector in a packaging cell; and

producing chimeric adenoviral particles.

38. (New) The method according to claim 35 wherein the first adenovirus serotype is serotype 5.

39. (New) The method according to claim 35 wherein the recombinant vector comprises a plasmid.

40. (New) A method for producing a chimeric adenoviral particle having a capsid derived from a first adenovirus serotype exhibiting a desired tropism and antigenicity determined by a part of a fiber derived from adenovirus serotype 35, the method comprising:

providing a recombinant vector derived from the first adenovirus serotype comprising at least one ITR, a packaging signal, an insertion site for a nucleic acid sequence of interest, and an insertion site for a gene encoding the functional part of the fiber protein of adenovirus serotype 35;

inserting into the vector the gene encoding the functional part of the fiber protein derived from adenovirus serotype 35, the functional part of the fiber protein comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus;

transfecting said vector in a packaging cell; and

producing chimeric viral particles.

41. (New) The method according to claim 40 wherein the first adenovirus serotype is serotype 5.

42. (New) The method according to claim 40 wherein the recombinant vector comprises a plasmid.

43. (New) A recombinant vector derived from a first adenovirus serotype comprising:

at least one ITR;

a packaging signal;

a first insertion site for a nucleic acid sequence of interest;

a second insertion site for functionally inserting a gene encoding a part of a fiber protein of a second adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50; and

a gene encoding the part of the fiber protein of the second adenovirus serotype inserted in the second insertion site, the part of the fiber protein of the second adenovirus serotype exhibiting a desired tropism to a plurality of cells in a host and comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus.

44. (New) The recombinant vector of claim 43 wherein the recombinant vector comprises a plasmid.

45. (New) The recombinant vector of claim 43 wherein the first adenovirus serotype is serotype 5.

46. (New) A recombinant vector derived from a first adenovirus serotype comprising:

at least one ITR;

a packaging signal;

a first insertion site for a nucleic acid sequence of interest;

a second insertion site for functionally inserting a gene encoding a part of a fiber protein of adenovirus serotype 35; and

a gene encoding the part of the fiber protein of adenovirus serotype 35 inserted in the second insertion site, the part of the fiber protein of adenovirus serotype 35 exhibiting a desired tropism to a plurality of cells in a host and comprising a tail region of a fiber of the first adenovirus serotype at its N-terminus.

47. (New) The recombinant vector of claim 46 wherein the recombinant vector comprises a plasmid.

48. (New) The recombinant vector of claim 46 wherein the first adenovirus serotype is serotype 5.